MASTOLOGY

Official Journal of the Brazilian Society of Mastology

Volume 33, 2023

ISSN 2594-5394

Brazilian Society of Mastology

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BRAZILIAN SOCIETY OF MASTOLOGY

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ABOUT

Mastology is a publication of the Brazilian Society of Mastology. The responsibility for concepts emitted in the articles is exclusive of its authors

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National and international subscription and advertising: Brazilian Society of Mastology - Phone number: (21) 2220-7711 - Whatsapp (21) 98138-0034

EDITORIAL PRODUCTION

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ORIGINAL ARTICLE
https://doi.org/10.29289/2594539420220041

Use of artificial intelligence to predict response to neoadjuvant chemotherapy in breast cancer

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ABSTRACT

Introduction: Breast cancer is the object of thousands of studies worldwide. Nevertheless, few tools are available to corroborate prediction of response to neoadjuvant chemotherapy. Artificial intelligence is being researched for its potential utility in several fields of knowledge, including oncology. The development of a standardized Artificial intelligence-based predictive model for patients with breast cancer may help make clinical management more personalized and effective. We aimed to apply Artificial intelligence models to predict the response to neoadjuvant chemotherapy based solely on clinical and pathological data. **Methods:** Medical records of 130 patients treated with neoadjuvant chemotherapy were reviewed and divided into two groups: 90 samples to train the network and 40 samples to perform prospective testing and validate the results obtained by the Artificial intelligence method. **Results:** Using clinicopathologic data alone, the artificial neural network was able to correctly predict pathologic complete response in 83.3% of the cases. It also correctly predicted 95.6% of locoregional recurrence, as well as correctly determined whether patients were alive or dead at a given time point in 90% of the time. To date, no published research has used clinicopathologic data to predict the response to neoadjuvant chemotherapy in patients with breast cancer, thus highlighting the importance of the present study. **Conclusions:** Artificial neural network may become an interesting tool for predicting response to neoadjuvant chemotherapy, locoregional recurrence, systemic disease progression, and survival in patients with breast cancer.

KEYWORDS: artificial intelligence; breast; breast neoplasms; neoadjuvant therapy; neoplasms.

INTRODUCTION

Despite being the object of thousands of studies worldwide and having the largest body of evidence to explain its pathophysiology among all cancer types, breast cancer (BC) continues to claim thousands of lives each year[1]. Many different and customizable treatment options are available for the various types of BC. One treatment strategy widely used in clinical practice is neoadjuvant chemotherapy (NACT)[2].

NACT consists of the preoperative administration of chemotherapeutic drugs with a view to reducing tumor size before surgery. Its use has been associated with improved prognosis. Currently, response to NACT cannot be measured or predicted by the clinician, which restricts decision-making regarding the appropriateness of this treatment option in individual cases. Tools that can predict the response to NACT could be practice-changing by helping define the most appropriate clinical management strategy for each patient[2,3].

Nevertheless, few tools are available to corroborate prediction of response to NACT. Two prediction tools are currently on the market, the 21-gene Oncotype DX® panel and the 70-gene MammaPrint®[4,5] panel, both based on the quantification of the expression of different genes known to be involved in the pathophysiology of BC. Oncotype and MammaPrint are representative and very important on the world stage; however, their applicability is limited by the high cost inherent in the quantitative analysis of gene expression.

Artificial intelligence (AI) is being researched for its potential utility in several fields of knowledge, including oncology.

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Conflict of interests: nothing to declare. **Funding:** PRONEX-FAPERGS/CNPq (Grant number 16/2551-0000473-0-1).
Received on: 09/28/2022. **Accepted on:** 12/19/2022.

The ability of a technology to receive information, process it, and make decisions based on that information can be very relevant in several aspects of the oncology practice, including the prediction of response to NACT. AI systems can currently receive and interpret clinical and pathological information about patients and predict possible outcomes based on cases from past examples, i.e., after learning about the subject[6-8].

The development of a standardized AI-based predictive model for patients with BC may help make clinical management more personalized and effective. In our study, we aimed to apply AI models to predict the response to NACT based solely on clinical and pathological data.

METHODS

a. Patients

All medical records of patients treated with NACT at the High Complexity Unit on Oncology (UNACON) of Hospital Geral de Caxias do Sul (RS), Brazil, and at an affiliated private clinic from March 2012 to June 2020 were reviewed. The records of 130 patients containing all clinicopathologic information of relevance to the study were analyzed and divided into two groups: 90 samples to train the neural network and 40 samples to perform prospective tests and validate the results obtained by the AI method.

b. Clinicopathologic criteria

The study included patients for whom the following information was available: age, body mass index, weight, height, menopausal status, histologic type, histologic grade, expression of estrogen (ER) and progesterone (PR) receptors, human epidermal growth factor receptor 2 (HER-2), expression of Ki-67, tumor size, axillary involvement, molecular subtype, clinical staging, chemotherapy protocol, progression during chemotherapy, targeted therapy, and pathologic staging.

Overall survival was analyzed from the date of diagnosis until the date of the last follow-up (for patients who remained alive) or date of death. Progression-free survival was analyzed from the date of diagnosis to the date of disease progression (for patients who experienced disease progression), date of death (for patients who died), or date of the last follow-up (for patients who remained alive). Pathologic complete response (PCR) was defined as absence of invasive carcinoma and/or carcinoma in situ in the breast, and ipsilateral axilla after NACT.

c. Expression of estrogen, progesterone, Ki-67 and HER-2 receptors

ER, PR, and HER expressions in breast biopsy specimens were evaluated by means of immunohistochemistry, with the following antibodies:

1. anti-ER MAb (Dako, Glostrup, Denmark, 1/100 dilution),
2. anti-PR MAb (Dako, 1/800 dilution), and
3. polyclonal anti-HER2 antibodies (Dako, 1/3200 dilution) for the HER-2-neu gene.

The scoring of ER and PR were based on the staining intensity (weak, moderate, intense). The evaluation criteria of HER2 status were based on immunostaining and the percentage of membrane positive cells, giving a score range of 1+, 2+, 3+. HER2 negative was categorical when no staining was observed or membrane staining was observed in 1–9% of tumor cells. HER2 was classified as score 2+ when there was a weak to moderate complete membrane staining in 10% to 49% of the tumor cells, while HER2 was positive score 3+ when there was a strong complete membrane staining in more than 50% of the tumor cells. In this study, HER2 scores 0 and 1+ were considered negative. HER2 3+ and the Amplified Fluorescence in situ Hybridization (FISH-amplified) tumors were considered positive. All HER2 2+ tumors and tumors for which immunohistochemistry (IHC) was not assessable were also tested for gene amplification by FISH.

Ki-67 labeling index was defined as the percentage of Ki-67 antigen positive cells, giving a score range low (<14%) and high (≥14%).

d. Analysis of tumor-infiltrating lymphocytes

The percentage of tumor-infiltrating lymphocytes (TILs) was assessed in paraffin-embedded tumor sections stained with hematoxylin and eosin (HE) and was defined as the percentage of lymphocytes in direct contact with tumor cells.

e. Artificial intelligence

AI is a growing science. Its core principle is the development of cognitive models that are capable of interpreting and forecasting data. This interpretation is based on the knowledge acquired by the model. Within AI science, "knowledge" is data[7].

Cognitive models are based on so-called artificial neural networks (ANNs), which simulate a biological neuron. Human neurons consist of several specific regions, as:

1. dendrites, which receive nerve impulses;
2. the cell body, or soma, in which information processing takes place; and
3. nerve endings, which are responsible for the output of nerve impulses.

An ANN has very similar regions, as seen in Figure 1 below. Its "dendrites" are represented by the letter *w*, which highlights the presence of more than one "nerve projection" (i.e., allowing receipt of more information), each differentially weighted to ensure a good data interpretation. In the "cell body" of the ANN, designated as *fa*, mathematical functions are applied to the data

obtained through *w*. Finally, "nerve endings" allow communication to take place between ANNs, simulating a neural synapse.

Clinicopathologic criteria were analyzed through the application of four ANNs composed of 200 neurons, each designed specifically for prediction of one of the following outcomes: PCR, locoregional recurrence, systemic disease progression, and death. The variables analyzed by the ANNs are described in Table 1.

Neural networks were created to analyze the outcomes of interest. These networks were trained on 90 samples and afterwards was prospectively tested on 40 additional samples.

f. Ethical aspects

As the present study consists of a retrospective analysis of data from medical records and does not involve direct intervention on human subjects, investigators were asked to sign a data use agreement and confidentiality form. Informed consent was waived.

g. Statistical analysis

After the identification of the core (indispensable) criteria, four supervised-learning ANNs were constructed using a pattern recognition tool. To ensure optimal fit, a backpropagation algorithm with feed-forward network topology was used to identify PCR, systemic disease progression, locoregional recurrence, and survival. To enhance ANN effectiveness, the number of neurons was tested with a variety of different settings. To evaluate whether the proposed system was effective, a prospective study was then carried out using the developed ANNs.

Descriptive analysis of clinicopathologic data was performed in SPSS 20.0 software (SPSS Inc. Chicago, IL, United States).

The Figure 1 illustrates the diagram with the methodologies used in this research.

Table 1. Variables used in the neural network.

	Values
Age (years)	Numeric
Body mass index	Numeric
Weight	Numeric
Height	Numeric
Menopausal status	Pre-menopausal or post-menopausal
Histologic type	Invasive lobular, invasive ductal, medullary, or other
Histologic grade	G1, G2, or G3
Estrogen receptor expression	Numeric
Progesterone receptor expression	Numeric
HER-2 expression	1+, 2+, 3+
Ki-67 expression	Low or high
Molecular subtype	Luminal A, luminal B, or HER2-enriched
Clinical staging	IA, IB, IIA, IIB, IIIA, IIIB, IIIC, IV
Chemotherapy protocol	Trastuzumab; lapatinib; pertuzumab; trastuzumab + pertuzumab; trastuzumab + lapatinib; other
Progression on chemotherapy	Yes or no
Neoadjuvant targeted therapy	None; trastuzumab; lapatinib; pertuzumab; trastuzumab +pertuzumab; trastuzumab+ lapatinib; other
Tumor size and location	Ductal carcinoma in situ, T1mi, T1a, T1b, T1c, T2, T3, T4a, T4b, T4c, T4d
Lymph nodes staging	N0, N1, N2, N3
Number of affected lymph nodes	Numeric

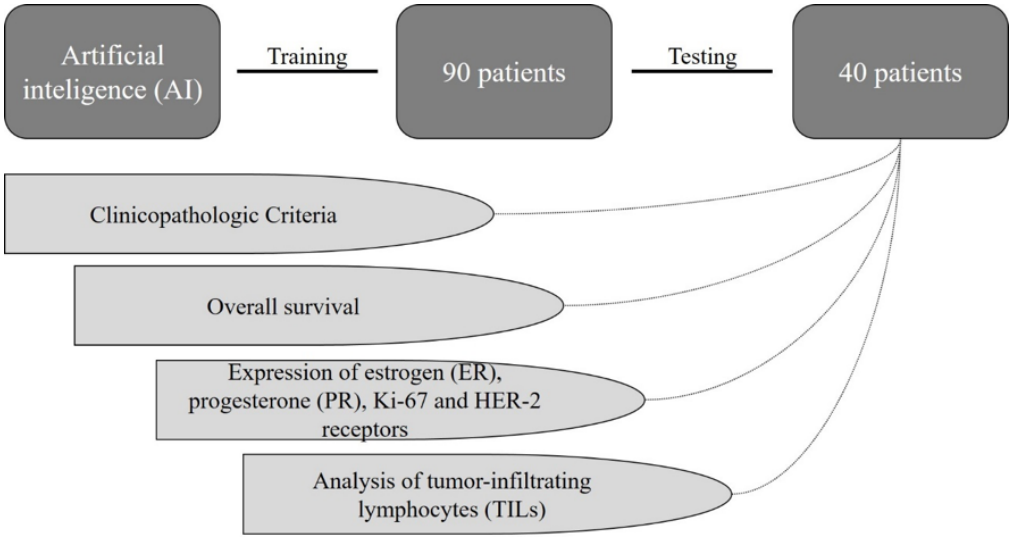

Figure 1. Diagram of methodologies used in this research.

RESULTS

Clinicopathologic data

A retrospective analysis of the medical records of 90 patients was carried out. The mean age at diagnosis was 46.3 years, and the mean body mass index was 27.0. Overall, 59 (65.6%) patients were pre-menopausal and 31 (34.4%) were post-menopausal. On histologic analysis, only 1 patient (1.1%) had invasive lobular BC, 73 patients (81.1%) had invasive ductal carcinoma, 5 (5.6%) had medullary carcinoma, and 11 (12.2%) had BC of other histological types. Most of the patients had histologic grade G3 tumors, totaling 48 (53.3%), 36 (40.0%) had grade G2, and only 6 (6.7%) had grade G1 (Table 2).

Regarding gene expression in biopsy specimens, 50 of 90 (55.6%) had biopsies strongly positive for ER, followed by 30 (33.3%) which were ER-negative. The rest of the biopsies showed low ER expression (2; 2.2%) and positive ER expression (8; 8.9%). As for PR expression, most biopsies were negative, being 39 (43.3%), followed by strongly positive expression in 31 (34.4%), positive expression in 18 (20.0%), and low expression in only 2 cases (2.3%) (Table 2).

Once HER2 expression was evaluated, 54 biopsies (60%) showed no expression and 36 (40.0%) showed 1+ expression. Furthermore, 87 biopsies (96.7%) showed high Ki67 expression. The molecular subtypes observed were: luminal B in 32 cases (35.6%), HER2-enriched in 24 (26.7%), triple-negative in 19 (21.1%), pure HER2 in 12 (13.3%), and luminal A in 3 (3.3%) (Table 2).

Of the 90 patients who received treatment, only 32 (35.6%) achieved PCR, while 58 (64.4%) did not. Fifteen patients (16.7%) experienced systemic disease progression, while 75 (83.3%) were progression-free (Table 2). This same analysis was performed in the prospective study (Table 2).

Artificial neural network performance evaluation

Clinicopathologic criteria were analyzed through application of an ANN composed of 200 neurons to predict the response to NACT. To assess predictive capacity, confusion matrices were generated. Sensitivity, specificity, false-positive rate, and false-negative rate were then derived.

With clinicopathologic data alone, the ANN was able to correctly predict PCR in 83.3% of cases, with 84.4% sensitivity, 82.8% specificity, a positive predictive value (PPV) of 73%, and a negative predictive value (NPV) of 90.6%. Tested prospectively, the ANN achieved an accuracy of 80.0%, sensitivity of 81.8%, specificity of 79.3%, and negative and positive predictive values of 92 and 60% respectively (Table 3).

When predictive capacity for systemic progression was assessed, the ANN exhibited 82.2% accuracy, with 0% sensitivity, and 98.7% specificity. The PPV was 0%, and the NPV, 83.1%. When prospectively tested, an accuracy of 77.5% was achieved, with sensitivity and specificity of 100% and 76.9%, respectively, and NPV of 100% and PPV of 10% (Table 3).

Table 2. Clinicopathologic data.

	n (%) retrospective	n (%) prospective
Age (years)	46.3	47.5
Body mass index	27.0	27.9
Weight	70.5	71.3
Height	1.6	1.6
Menopausal status		
Pre-menopausal	59 (65.6)	27 (67.5)
Post-menopausal	31 (34.4)	13 (32.5)
Histologic type		
Invasive lobular	1 (1.1)	0 (0)
Invasive ductal	73 (81.1)	37 (92.5)
Medullary	5 (5.6)	2 (5)
Other	11 (12.2)	1 (2.5)
Histological grade		
G1	6 (6.7)	5 (12.5)
G2	36 (40)	19 (47.5)
G3	48 (53.3)	16 (40)
Estrogen receptor expression		
None	30 (33.3)	17 (42.5)
Low	2 (2.2)	0 (0)
Positive	8 (8.9)	3 (7.5)
Strongly positive	50 (55.6)	20 (50)
Progesterone receptor expression		
None	39 (43.3)	19 (47.5)
Low	2 (2.3)	0 (0)
Positive	18 (20)	7 (17.5)
Strongly positive	31 (34.4)	14 (35)
HER2 expression		
0	54 (60)	33 (82.5)
1+	36 (40)	7 (17.5)
2+	0 (0)	0 (0)
Ki67 expression		
Low	3 (3.3)	7 (17.5)
High	87 (96.7)	33 (82.5)
Molecular subtype		
Luminal A	3 (3.3)	5 (12.5)
Luminal B / HER2-negative	32 (35.6)	15 (37.5)
Luminal B / HER2-enriched	24 (26.7)	3 (7.5)
Pure HER2	12 (13.3)	4 (10)
Triple negative	19 (21.1)	13 (32.5)
Pathologic complete response	32 (35.6)	15 (37.5)
No pathologic complete response	58 (64.4)	25 (62.5)
Systemic progression	15 (16.7)	10 (25)
No systemic progression	75 (83.3)	30 (75)

The same analysis was performed for locoregional recurrence. The ANN had 95.6% accuracy, with a sensitivity of 0% and specificity of 100%. Positive and negative predictive values were 0% and 95.6%, respectively. In the prospective test, the network accuracy was 95%, with sensitivity and specificity of 0% and 95%, respectively. The PPV was 0% and the NPV was 100% (Table 3). The sensitivity and PPV were 0% because no patient had disease progression or recurrence in the retrospective dataset.

When the ANN was used to predict whether patients would be alive or dead, it achieved 90% accuracy, with a sensitivity of 95.1%, and specificity of 44.4%. Positive and negative predictive values in this analysis were 93.9 and 50%, respectively. Tested prospectively, the ANN achieved an accuracy of 87.5%, sensitivity of 94.3%, specificity of 40%, NPV of 50%, and PPV of 91.7% (Table 3).

DISCUSSION

NACT is associated with PCR as well as with locoregional or systemic recurrence, and the response to NACT is the main determinant of each of these events. The present study demonstrated, for the first time, how the response to NACT can be predicted with AI methods. AI is a growing area of study, with an ever-increasing body of evidence demonstrating its applicability in various fields[6-8]. The possibility of using an AI tool to guide clinical management of BC, a life-threatening condition, is extremely relevant.

Neoadjuvant Chemotherapy and Pathologic complete response

PCR is associated with several factors. Understanding which are these factors and the relative importance of each one is essential. In this study, clinicopathologic data were used to train an ANN to predict response to NACT. Corroborating the present study, prior researches have described various clinical and pathologic factors that may be related to the response to NACT. Díaz-Casas et al.[9], in a study of 414 patients with BC, found that PCR was associated with tumor molecular type, observing higher rates of PCR in pure-HER2 and triple-negative tumors. They also found that larger tumors are associated with nonresponse to NACT.

When analyzing clinicopathologic predictors of recurrence in patients with BC who achieved PCR to NACT, advanced clinical staging, tumor size, presence of lymph node metastases, and HER2 positivity before NACT were identified as significantly predictive of disease recurrence. Conversely, residual ductal and nodal disease in situ after NACT were not significant predictors[10].

In a study of 117 patients, PCR was significantly associated with expression of ER and absence of HER2 expression (p=0.0006), as well as with stages T2 (p=0.043) and T3 (p=0.018)[11]. The same factors were assessed in our study and, corroborated as predictive of PCR. We used data to construct an ANN and predict the same outcome previously described in the literature, Thus, our results corroborate the data published in the literature, but with a significant difference: the use of AI to obtain them.

Neoadjuvant chemotherapy and locoregional recurrence

In our study, the ANN correctly predicted locoregional recurrence 95.6% of the time, with a NPV of 95.6%. These data were obtained through the use of an AI model based on clinicopathologic data only. This same correlation was described in a large study involving 3,088 patients over a 10-year follow-up period, which found that the clinical characteristics of a tumor can be used to predict the risk of locoregional recurrence[12]. The same association was observed by Gillon et al. in 1,553 patients; the authors reported that BC classification and PCR are important predictors of locoregional recurrence[13].

To date, there are no reports of the use of AI to predict locoregional recurrence in patients with BC after NACT. Therefore, this is the first study to demonstrate a new predictive model with the potential to change clinical management.

Neoadjuvant chemotherapy and systemic disease progression

Death after NACT is associated with progression of systemic disease. The ANN correctly predicted whether patients would be alive or dead after NACT 82.2% of the time, with a specificity of 98.7%; on subsequent prospective testing, 77.5% accuracy was achieved. Several factors have been described in the literature

Table 3. Predictive performance of an artificial neural network trained on clinicopathologic data alone to assess response to neoadjuvant chemotherapy in patients with breast cancer.

	Pathologic complete response		Systemic progression		Locoregional recurrence		Survival	
	Retro (%)	Prosp (%)	Retro (%)	Prosp (%)	Retro (%)	Prosp (%)	Retro (%)	Prosp (%)
Accuracy	83.3	80	82.2	77.5	95.6	95	90	87.5
Sensitivity	84.4	81.8	0	100	0	0	95.1	94.3
Specificity	82.8	79.3	98.7	76.9	100	95	44.4	40
Positive predictive value	73	60	0	10	0	0	93.9	91.7
Negative predictive value	90.6	92	83.1	100	95.6	100	50	50

Retro: retrospective; Prosp: prospective.

as potential predictors of systemic progression. HER-2 expression and triple-negative status are two factors reported as such by Yiqun et al.[14].

A previous study evaluated the ability of an ANN to predict survival after BC without assessing the response to NACT. Based only on the Surveillance, Epidemiology, and End Results (SEER) Program[15] dataset, composed of 162,500 records with 16 main characteristics (the most informative ones being tumor size, number of affected lymph nodes, and age at diagnosis, all parameters which were also included in our model), this ANN achieved 65% accuracy[16].

Artificial intelligence-based forecasting

The use of AI in healthcare has been growing exponentially, with particular interest in the development of systems to guide clinical management. Specifically regarding BC, studies have focused on the ability of AI to interpret imaging findings[17-19]. There is very little published data on chemosensitivity and resistance[7,20], and, so far, no studies have demonstrated predictive ability based exclusively on clinicopathologic data. The present study is thus the first of its kind.

Some prior research has investigated the ability of ANNs and their learning models to predict risk in BC, including disease progression[21-25]. However, to date, no published research has used clinicopathologic data to predict the response to NACT in patients with BC, thus highlighting the importance of the present study in advancing science.

Limitations include the lack of validation of the model in a larger sample, which justifies the expansion of the present project. For this reason, we have requested this extension in an effort to minimize its limitations and hence contribute more significantly to the clinical management of patients with BC.

CONCLUSIONS

Breast cancer is a heterogeneous and complex disease. Considering their ability to adapt, learn from examples, organize data, and recognize patterns, ANNs may become an interesting tool for predicting response to NACT, locoregional recurrence, systemic disease progression, and survival in patients with BC.

AUTHORS' CONTRIBUTION

KOBG: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MCK: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing. BC: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Software, Validation, Visualization, Writing – review & editing. LLC: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Software, Validation, Visualization, Writing – review & editing. MRE: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. JAPH: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing. JB: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing

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CASE REPORT
https://doi.org/10.29289/2594539420210037

Salivary gland tumor: atypical presentation of breast cancer

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ABSTRACT

Breast cancer is a heterogeneous disease with various histological and molecular subtypes. Among them, salivary gland tumors are rare and can be divided into three groups: pure myoepithelial differentiation, pure epithelial differentiation and myoepithelial with mixed epithelial differentiation. In the last group, adenoid cystic carcinoma stands out, a rare entity with low malignant potential. It represents less than 0.1–3% of breast cancer cases and has the most frequent clinical presentation as a palpable mass. The diagnosis is confirmed by histology and immunohistochemistry. Classically, they are low-aggressive triple-negative tumors, with overall survival and specific cancer survival at five and ten years greater than 95%. However, there are rare reports of aggressive variants with a risk of distant metastasis and death. Treatment is based on surgical resection with margins. Lymphatic dissemination is rare, and there is no consensus regarding the indication of an axillary approach. Adjuvant radiotherapy is indicated in cases of conservative surgery and should be discussed in other cases. The benefit of chemotherapy remains uncertain, as most tumors are indolent. We report a case that required individualized decisions based on its peculiarities of presentation, diagnosed in an asymptomatic elderly patient during screening, in which mammography showed heterogeneous gross calcifications clustered covering 1.6 cm. Stereotactic-guided vacuum-assisted biopsy was performed, and the area was marked with a clip. The anatomopathological examination led to a diagnosis of salivary gland-type carcinoma, triple-negative. The patient underwent segmental resection of the right breast and sentinel lymph node biopsy. The final anatomopathological result was similar to that of the biopsy, with an immunohistochemical profile of the adenoid cystic type and two sentinel lymph nodes free of neoplasia. Considering age and histological subtype, adjuvant therapy was not indicated. Follow-up for three years showed no evidence of disease.

KEYWORDS: breast cancer; triple-negative breast cancer; adenoid cystic carcinoma.

INTRODUCTION

Breast cancer is the most common malignant disease in women[1], considered a heterogeneous disease with various clinical and pathological presentations[2], and among them, salivary gland tumors are rare. These can be divided into three groups: pure myoepithelial differentiation, pure epithelial differentiation and myoepithelial and mixed epithelial differentiation. In the last group, adenoid cystic carcinoma stands out, a rare entity with low malignant potential[3].

Adenoid cystic carcinoma (ACC) of the breast is a heterogeneous biphasic tumor composed of basaloid and epithelial cells. It represents approximately 0.1–3% of breast cancers[4,5]. Due to its rarity, there are few databases on this carcinoma, and most of the studies are case reports or with a small sample of patients. The management protocol remains unestablished. Therefore, to contribute to the formation of a database about the ACC, we report a case of an elderly patient diagnosed during screening, requiring individualized decisions based on their peculiarities of presentation.

CASE REPORT

A 74-year-old woman, menopausal, history of sister with breast cancer at age 58, presented to the outpatient clinic asymptomatic, and she was referred because of changes in the screening mammogram. Mammography (Figure 1) showed heterogeneous gross calcifications clustered in the superolateral quadrant of the right

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Conflict of interests: nothing to declare. **Funding:** none.
Received on: 07/29/2022. **Accepted on:** 12/19/2022.

breast, measuring 1.6 cm, classified as BIRADS 4. A percutaneous vacuum-assisted biopsy guided by stereotaxis was performed, and the area was marked with a clip. The anatomopathological result showed a salivary gland-type carcinoma, histological and nuclear grade 2, with an immunohistochemical profile showing positive C-kit, CK5/6 and S-100 and negative hormone receptors and HER-2 (triple-negative).

Because of the favorable histology and extent of the disease, the patient was then submitted to segmental resection of the right breast and sentinel lymph node biopsy. The final anatomopathological result (Figure 2) confirmed that it was an invasive carcinoma of the salivary gland type, with a morphological and immunohistochemical pattern of the adenoid cystic type, histological and nuclear grade 2, measuring 2.2 x 1.5 cm, associated with flat and solid ductal carcinoma ***in situ,*** with deep and inferior margin compromised by the invasive neoplasia and two sentinel lymph nodes free of neoplasia. The patient then underwent enlargement of surgical margins, with multifocal residual invasive neoplasia, the largest focus measuring 0.81 cm, with free margins and the presence of angiolymphatic embolization. Considering age and histological subtype, adjuvant therapy was not indicated. She was followed up for three years and then had no evidence of disease.

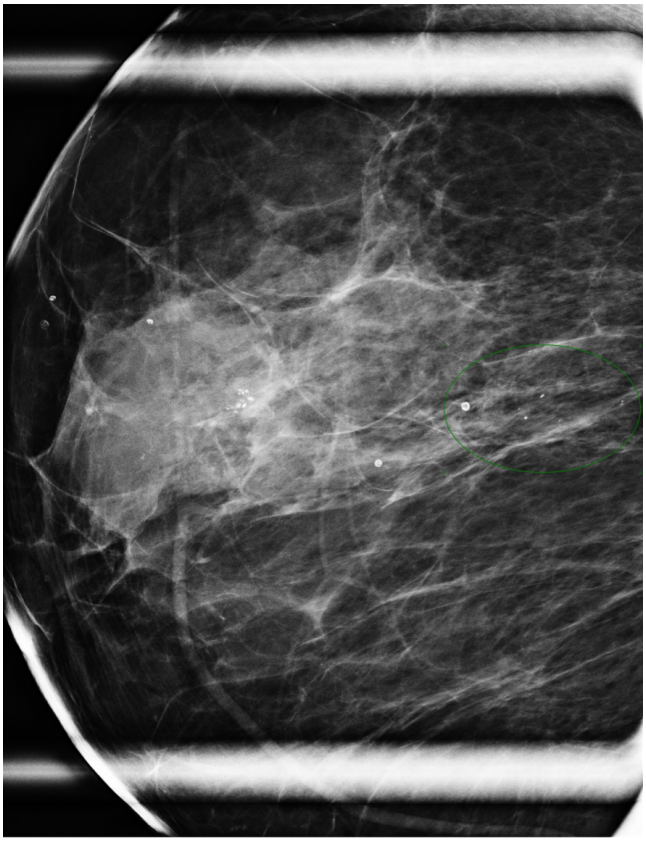

Figure 1. Calcification clustered in the superolateral quadrant of the right breast.

DISCUSSION

Clinico-pathological characteristics

ACC is a characteristically biphasic subtype of salivary gland tumor, composed of myoepithelial/basaloid and luminal/epithelial ductal cells, which can be arranged in tubular, cribriform or solid growth patterns[3,5,6]. Generally, there are these three patterns in the same tumor, present in heterogeneous proportions, the tumor being graded by the extent of the solid component[6]. Within this morphological spectrum of presentation, the basaloid predominant variants tend to have greater tumor aggressiveness[3,7].

On microscopic analysis, the cells of this tumor have scarce cytoplasm and a hyperchromic nucleus[6], but a variable spectrum of morphological aspects, similar to those seen in salivary glands, is reported, impacting the prognosis[3].

Genetically, ACC is characterized by a specific gene fusion, responsible for the development of its characteristic phenotype. The case in question had an infrequent presentation of adenoid cystic carcinoma (suspicious calcifications) on screening mammography[6].

This tumor is characterized by an insidious and continuous evolution[6], usually diagnosed in the early stages[4,5,8], as in the case of the patient in this report. The most common clinical presentation is a palpable mass/nodule, present in up to about 70% of cases[2,3,5]. The atypical presentation of the reported patient can be seen, who was asymptomatic, with a change in the screening examination.

Zhang et al. reported in a retrospective cohort and meta-analysis with a sample of 511 that more than half of diagnoses occur in patients between 50 and 69 years old[8], which is compatible with data from several other studies[2,4,5] and similar to that observed in American databases[9]. Our patient was slightly above this age range, as she was 74 years old at the time of diagnosis.

The rate of patients with a family history of breast cancer, suggesting a hereditary component, is similar to that usually described for invasive ductal carcinoma of no special type (IDC-NST).

The radiological findings are variable and may be difficult to interpret[2,3]. A suggestive sign on imaging is the presence of an isodense mass with internal septations on magnetic resonance imaging in the T2-weighted sequence[10]. The reported patient had a peculiar presentation, with a mammogram showing clustered heterogeneous coarse calcifications.

Preoperative diagnosis can be performed with fine-needle or core-needle biopsy, the latter being more accurate[3].

Immunohistochemistry helps in the diagnosis and explains the heterogeneity of the cells that make up the ACC: epithelial cells express CK7, CK8 and CD117(c-Kit); basaloids express CK14 and CK5/6; the myoepithelial ones express S-100[2-5]. As for the molecular classification, the vast majority are triple-negative[2-5,8]. However, there are controversies in the literature, with

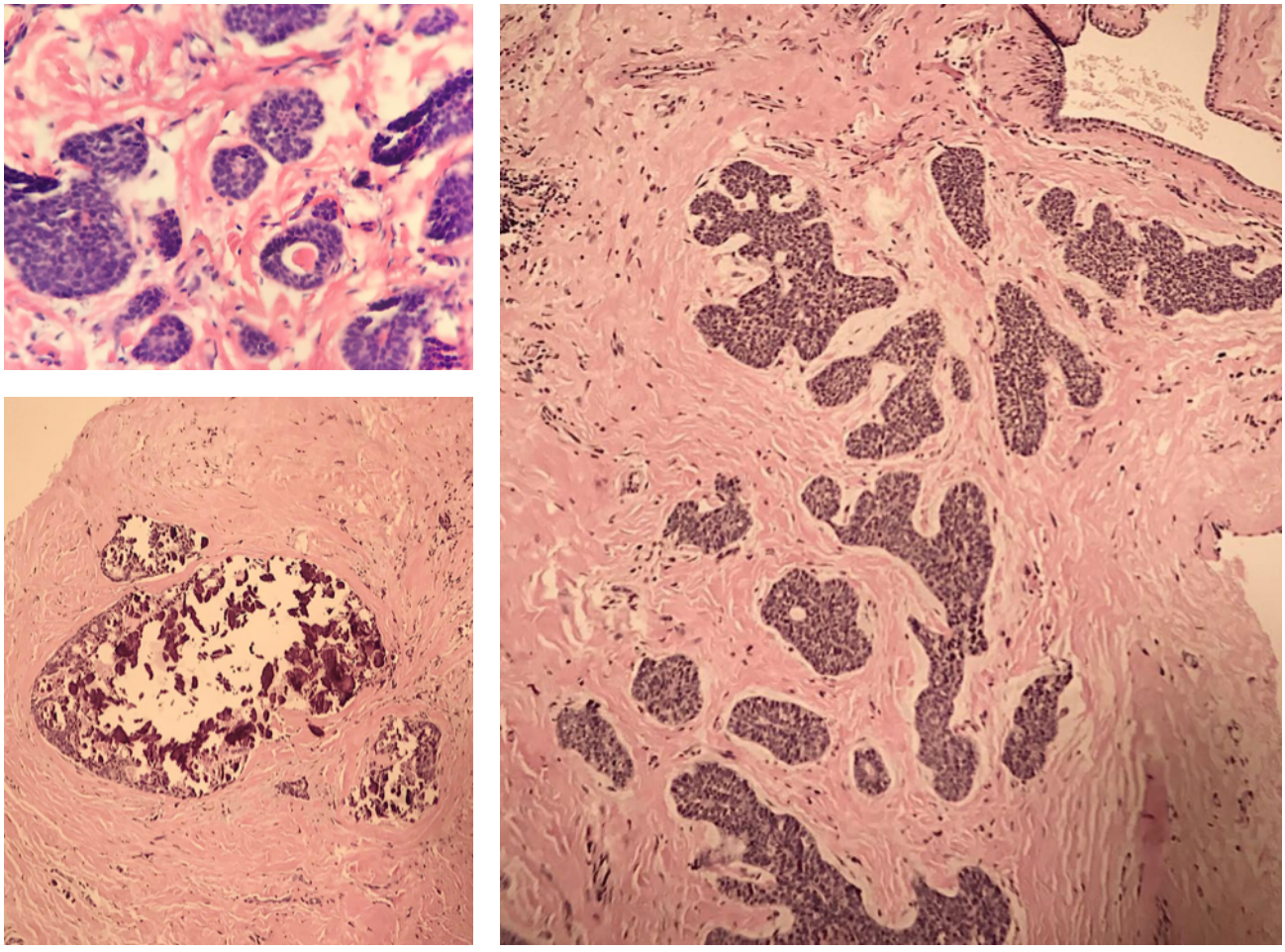

Figure 2. Histological pattern of the tumor.

the frequency of hormone receptor positive tumors ranging from 25%[11] to almost 50%[12]. The tumor in the reported case was triple-negative, fitting the most common form of molecular classification of this tumor subtype, and exhibited immunohistochemical expression of the markers mentioned in the literature, with c-Kit, CK5/6 and S-100 being positive.

Most triple-negative breast tumors are aggressive, with a high histological grade. However, ACC tends to have a favorable prognosis and low histological grade, even when it presents as triple-negative[2]. It is suggested that this is due to the lower Ki-67 rate, but there is still controversy in the literature[2]. Another study suggests that this association is due to the lower genomic instability of ACC[13].

Still, ACC may rarely undergo a process of dedifferentiation from the neoplastic clone, with the development of more aggressive high-grade carcinomas and with a greater risk of distant metastasis[3].

Treatment and prognosis

There are no well-established management protocols because of the sampling limitations of studies due to the rarity of this pathology[2,3]. Classically, treatment involves surgery with resection margins, with conservative surgery considered an adequate therapeutic option[14], always followed by adjuvant radiotherapy[2,6,14]. Zhang et al. reported a conservative surgery rate of 66%. The patient in the reported case underwent conservative surgery with assessment of intraoperative margins, which were compromised, leading to a reapproach for enlargement. Adjuvant radiotherapy followed[8].

Mastectomy may be indicated if the invasive lesion with tumor is affecting the breast in a proportion that makes an aesthetically satisfactory partial excision unfeasible[2]. In the literature, the percentage of patients undergoing mastectomy ranged from 33 to 72%[2-5,8].

An important consideration in therapeutic choice is the knowledge that there are tumor variants that can be more aggressive, such as those with a basaloid predominance. This graduation is given by the proportion of distribution of the histological components (tubular, cribriform and solid)[3]. In these aggressive basaloid variants, the rate of nodal involvement can reach 20% and that of distant metastasis, 16%[3,15].

In general, lymphatic dissemination is rare, ranging from 0 to 5% in the literature[2,4,6,8,14,16]. Khanfir et al. reported no nodal involvement in a sample of 51 patients[14]. Because of this low rate of nodal involvement, the role of axillary dissection remains

unclear[2,14]. Sentinel lymph node biopsy may be an option, with good identification rates. To decide on its use, factors such as tumor size, hormone receptor status, nuclear grade and lymphovascular invasion should be evaluated[16]. In recent studies, the rate of performance of this procedure varied between 50 and 100%[4,5]. In the present case, we opted for sentinel lymph node biopsy, whose anatomopathological examination identified two cancer-free lymph nodes.

The use of adjuvant chemotherapy is controversial but should be considered[7]. In the consensus of St. Gallen in 2011, indicating adjuvant chemotherapy was suggested for cases of high-grade tumors, tumors larger than 3 cm, lymph node involvement or distant metastasis[17]. However, this tumor is usually resistant to this therapy[6], which is why its indication is rarely described[4,8].

Wang et al. compared 36 cases of ACC with 108 cases of low-grade breast invasive ductal carcinoma, with standardized groups regarding clinical and tumor variables. These authors concluded that ACC has a lower rate of Ki-67 and tumor nodal involvement but larger-size tumor compared to low-grade IDC-NST[2].

Classically, ACC is described as being associated with a favorable prognosis, with a low rate of distant metastasis and local recurrence, with excellent survival rates[2,4,8,18]. It should be noted that some studies are controversial, perhaps because of the heterogeneity and rarity of ACC, reporting rates of local recurrence and distant metastasis varying between 8 and 14% and 8 and 21%, respectively[2,6,15]. The most common sites of distant metastasis are lung, bone and liver[2,5].

Overall survival at 10 and 15 years exceeds 90%[2], with no difference in overall or disease-free survival in relation to that described for low-grade IDC-NST[2,18]. In a study with 511 patients, Zhang et al. reported overall and cancer-specific survival at five and ten years of 95.7 and 100%, respectively[8].

Some predictive factors of recurrence-free survival are described, such as positive margin, neovascularization, basaloid variant, perineural invasion, lymphovascular invasion, >30% solid component, lymph node involvement and presence of necrosis[15].

CONCLUSIONS

ACC is a rare subtype of breast cancer, and knowledge about its peculiarities is important to guide the correct diagnosis and management. Although most triple-negative tumors are considered more aggressive, ACC is indolent and considered to have a good prognosis.

Because of its rarity, there are few and low-sample studies, subject to a higher risk of bias. Therefore, there is no consensus on the treatment to be followed, making it necessary to create management protocols. Individualized therapeutic choice is recommended, assessing the risk x benefit of each approach.

AUTHORS' CONTRIBUTIONS

MLN: Writing – original draft, Writing – review & editing. TFSD: Project administration, Supervision, Writing – original draft, Writing – review & editing. GAC: Data curation, Investigation, Methodology. FEMA: Project administration, Supervision.

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ORIGINAL ARTICLE
https://doi.org/10.29289/2594539420220037

Evaluation of clinical, pathological and epidemiological profile of patients with breast cancer in the microregion of Lavras – MG

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ABSTRACT

Introduction: Breast cancer is associated with high frequency and mortality in Brazilian women. There have been limited studies portraying the characteristics of breast cancer cases in the countryside of the state of Minas Gerais for a long period of time, a fact that will allow us to better understand the epidemiology of these tumors. This descriptive study aims to analyze the epidemiology and clinical features of patients with breast cancer treated at a public health service facility in Lavras, MG. **Methods:** This is a transversal study with 299 women diagnosed with breast cancer between 2002 and 2022, based on data collection from medical records and subsequent descriptive analysis. **Results:** There were a total of 317 cases, and 299 were eligible for the study. The mean age at diagnosis was 54.2 years, and 36.1% of the patients were under 50 years old at diagnosis. Positive family history was found in 17.0% of the patients. The diagnosis was made by clinical alteration detected on physical examination in 71.5% of cases, and lump was the most frequent type of lesion (89.0%). Invasive carcinoma was 93.1% of the cases, and the mean tumor size was 28.6 mm. The average time between first medical appointment and diagnosis was 63.2 days, and between diagnosis and beginning of treatment was 39.6 days. **Conclusions:** This study showed that a significant number of cases occurred in women outside the recommended age for screening in Brazil. Diagnosis was predominantly performed by clinical examination, with delays in obtaining the histological diagnosis, and the stage at diagnosis was high, and these facts were associated with the health system limitations.

KEYWORDS: breast neoplasm; age groups; cancer screening.

INTRODUCTION

Breast cancer (BC) is the most common malignant neoplasm among women in Brazil and in the rest of the globe, accounting for 23% of all cancer cases worldwide[1,2]. Several risk factors have already been established, including endogenous and environmental factors. It is the leading cause of death from cancer in the Brazilian female population[3].

In the United States, BC mortality rates showed a 40% decline from 1989 to 2017, meaning over 375,000 fewer deaths[4]. In contrast, as is the case in most low- and middle-income countries, Brazilian estimates indicate stable or increasing mortality rates, with more than 16,000 deaths in 2017[5].

Early diagnosis is closely related to imaging diagnosis and clinical recognition of small tumors, strongly influencing the prognosis of the disease. According to Records from the Cancer Hospital, in Brazil there were 40% of BC diagnoses in stage 3 and 4 in 2010[6], Advanced stage at diagnosis is difficult and costly to treat, and is associated with increased morbidity and poor survival[7,8].

Among the prognostic factors, besides the intrinsic tumor characteristics, such as the hormonal receptors status and the human epidermal growth factor receptor-type 2 (HER2) overexpression, associated with the tumor size, axillary status, and staging, the time between the clinical manifestation of the disease and its diagnosis and initiation of treatment may be included[9,10].

The state of Minas Gerais has few and short isolated studies that portray the profile of patients with BC, as well as stage at diagnosis, time to obtain the diagnosis and to start treatment. Faced with such an incident pathology that causes significant morbidity and mortality among the female population in Brazil, studies must be conducted to better elucidate epidemiology, disease presentation and behavior, and the best methods involved in the screening and diagnosis of this disease[9,10].

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Conflict of interests: nothing to declare. **Funding:** none.
Received on: 09/01/2022. **Accepted on:** 01/03/2023.

The justification for carrying out the present study is based on the proposal to present the unprecedented results of a series of patients with BC in the microregion of Lavras, Minas Gerais.

The purpose of this article is to verify clinical and pathological characteristics, age distribution, as well as the time interval for the diagnosis and the beginning of treatment, of patients with breast cancer attended in the public service at a secondary reference center in the countryside of Minas Gerais (MG). Such knowledge may, thus, subsidize the planning, implementation, and evaluation of policies and actions of the Unified Health System (SUS) at the regional level, especially regarding the availability of methods that enable early detection and adequate treatment by the SUS.

METHODS

A descriptive, retrospective study was carried out based on the analysis of medical records of patients attended at the Mastology Service of the *Centro Estadual de Atenção Especializada* (CEAE) in the city of Lavras, in the south of the state of Minas Gerais, Brazil. The CEAE is a secondary care center, a reference in mastology care in the microregion of Lavras. It offers mastology appointments, imaging tests (mammography and ultrasound) and breast biopsies. Breast cancer surgeries are performed at *Santa Casa de Misericórdia de Lavras* – MG, and adjuvant treatments (chemo and radiotherapy) are provided in a reference center for the microregion in another city (Varginha, Minas Gerais).

People included in the study came from Lavras and its microregion, which comprises 10 other municipalities. Data were collected in a standardized form and, subsequently, tabulated and analyzed exposing quantitative variables and absolute and relative frequencies.

This study was approved by the Ethics Committee in Research with Human Beings of *Universidade Federal de Lavras* – MG (UFLA) – CAAE: 36285320.2.0000.5148.

All cases of breast carcinoma diagnosis between January 2002 and April 2022 were selected. The inclusion criterion was the histologic diagnosis of breast carcinoma in patients over 18 years of age. There were a total of 317 cases during the established period, 18 of which were excluded because there was no information in their records to obtain the necessary data and/or because they had undergone treatment at another health facility soon after diagnosis. Thus, the final sample of the study consisted of 299 patients.

Only cases of first-degree relatives with the disease, i.e., mother, sister and/or daughter, were considered as a positive family history. For the classification of the menopausal status, the definition of post-menopause was used, involving the classification of the patient into one of these four groups: women aged 60 years or older, women who underwent bilateral oophorectomy, women without their uterus and with laboratory tests showing increased follicle-stimulating hormone (FSH) levels, and women younger than 60 years of age, with uterus, non-users of hormonal therapy, in amenorrhea for at least 12 months before the diagnosis of breast cancer. Other than the situations described, the classification was premenopausal.

To obtain data for staging, classification of Tumor, Node, Metastasis (TNM), the 8th edition of the American Joint Committee on Cancer (AJCC) was used.

Molecular classification was based on luminal A (ER+/PR+/HER2-/low Ki-67: <20%), luminal B Her2-negative (ER+/PR+/HER2-/high Ki-67: ≥20%), luminal B Her2-positive (ER +/PR+/HER2+), Her 2 (ER-/PR-/ HER2+), and triple negative (ER-/PR-/HER2-) BC subtypes[11]. Positive ER or PR was considered when ≥1% of invasive malignant cells exhibited nuclear staining or immunoreactivity. The HER2 test was scored from 0 to 3+, where: score 0 or 1 was negative; 2+ was undefined; and 3+ was positive. When there was any undefined result, FISH (Fluorescence in situ hybridization) was performed for definition.

Database, analysis of variance and mean tests, as well as procedures for frequency analysis, were performed by the software Sisvar 5.3 Build 77.

RESULTS

In the final sample of the study, 299 patients with breast carcinoma were included; 204 of them were from the city of Lavras and the other 95 were from cities in the microregion.

The average age of the patients was 54.2 years (±12.3). The division into groups by age is shown in Figure 1.

The evaluation of the menopausal status showed that 40.5% of the patients were premenopausal at diagnosis. As for parity, 14.4% of the patients were nulliparous at the time of diagnosis. Positive family history was found in 17.0% of the cases. Clinical characteristics are listed in Table 1.

The diagnosis of breast cancer was given based on alterations in the clinical examination in 71.5% of the cases. Lump was the most common type of lesion found: 89.0% of the cases (Figure 2).

In this study, 93.1% of the patients had invasive breast carcinoma, and 6.9% were diagnosed with ductal carcinoma *in situ*. In cases of invasive carcinoma, the analysis of the histological type revealed the high prevalence of the ductal type: 84.5% of the cases (Figure 3).

The mean tumor size of invasive carcinomas was 28.6 mm (±19.5; 0.3–13.3 cm) and median of 25 mm. At the time of diagnosis, 56.9% of the patients had clinically negative axilla, and 43.1% had clinically positive axilla. Regarding the histologic grade, most patients had a lesion with histologic grade 2 (59.4%). Histopathological characteristics are listed in Table 2. The most common stages at the time of diagnosis were IIA and IA: 28.9 and 24.4%, respectively (Table 3).

The average time between the medical appointment that motivated the investigative process and the histologic diagnosis was

66.2 days (±48.0). The average time between the histologic diagnosis and the beginning of the treatment was 39.6 days (±29.8).

DISCUSSION

Breast cancer is a disease of global impact, high incidence, prevalence, and mortality. In Brazil, 66.280 new cases were estimated for 2022, which represents an adjusted incidence rate of 43.74 cases per 100,000 women[5]. For the same period, 8,250 new cases were estimated in Minas Gerais[5].

In this study, the mean age at diagnosis was 54.2 years. The highest frequency of cases occurred in women of the 50–59 age group (30.4%; n=91), but the high prevalence of cases among women aged 40–49 years stands out (25.4%; n=76). Combined with the cases of the 30-39 age group, they represent 34.8% of the total figure, a rather significant number of cases. The data evidenced

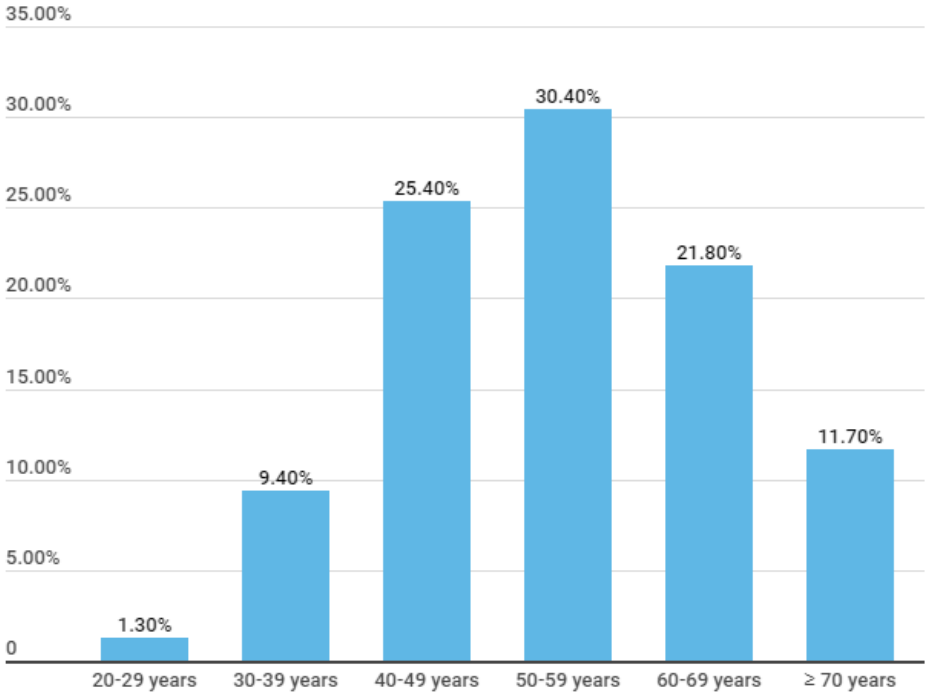

Figure 1. Distribution of breast cancer cases by age.

Table 1. Clinical characteristics of patients diagnosed with breast carcinoma.

	Category	Absolute frequency (n)	Percentage (%)
Parity	Nulliparous	43	14.4
	Primiparous	42	14.0
	Multiparous	214	71.6
Breastfeeding	Yes	231	77.3
	No	68	22.7
Menopausal status	Pre-menopause	121	40.5
	Post-menopause	178	59.5
Smoking	Yes	75	25.0
	No	224	75.0
Family History	Positive	51	17.0
	Negative	248	83.0
Type of Diagnosis	Clinical	214	71.5
	Imaging	77	28.5

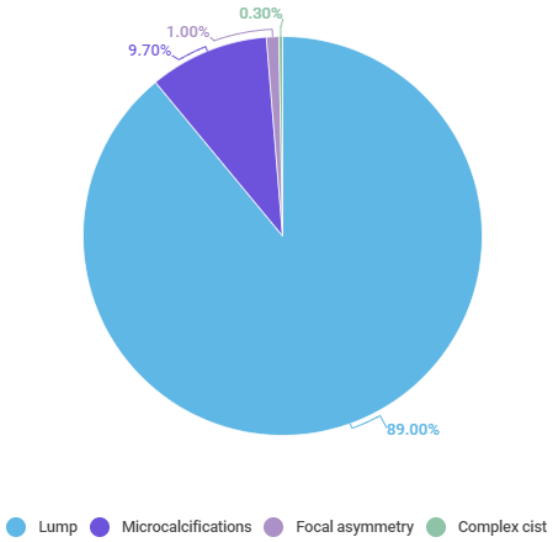

Figure 2. Type of lesion at disease presentation.

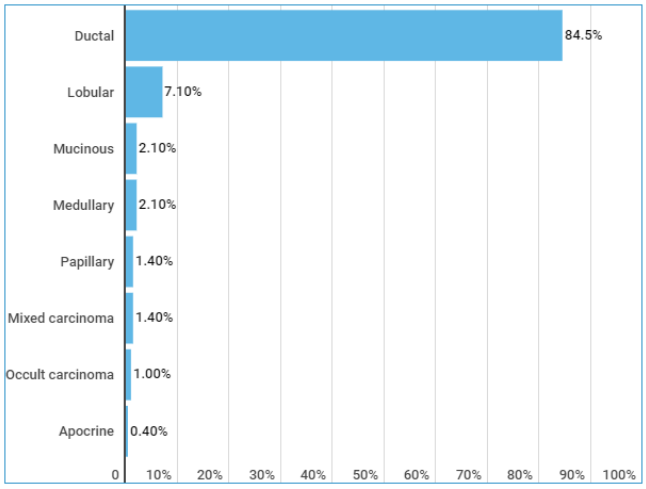

Figure 3. Distribution according to the invasive breast carcinoma histological type.

here are in agreement with other studies in the literature[12-14] Vale *et al.* found a prevalence of 34.4% in women under 50 years of age when surveying the number of breast cancer diagnoses given in the city of São Paulo between 2000 and 2015[15]. In the largest retrospective study on the breast cancer profile in the Brazilian population, called AMAZONA study, 41.1% of the patients were younger than 50 years old at the time of their diagnosis[16]. Such evidence raises the discussion regarding the need to expand the current screening program for breast cancer as adopted by the Ministry of Health in Brazil, which does not contemplate women between 40–49 years of age when they are at the usual risk. The high number of cases in women in this age group calls for greater attention for this public.

As for the histological type, it is known that the invasive ductal breast carcinoma, now called invasive carcinoma of no special type, is the most frequent subgroup, and the findings of this study are in line with the literature data[17]. The rate of ductal carcinoma *in situ* (DCIS) found was 6.9%. In Brazil, little information has been published on the epidemiology of carcinomas *in situ*. Its incidence is estimated to vary between 6.6 and 8.9%[12,18,19].

Table 3. Stage at diagnosis.

Stage	Absolute Frequency (n)	Percentage (%)
0	20	6.9
IA	71	24.4
IB	3	1.0
IIA	84	28.9
IIB	50	17.2
IIIA	33	11.3
IIIB	18	6.2
IIIC	5	1.7
IV	7	2.4

Table 2. Histopathological characteristics of the tumor.

Variable	Category	Absolute Frequency (n)	Percentage (%)
Estrogen receptor	Positive	234	81.5
	Negative	53	18.5
Progesterone receptor	Positive	215	74.9
	Negative	72	25.0
HER-2 Receptor	Positive	49	17.1
	Negative	237	82.9
Molecular Subtype	Luminal A	90	31.6
	Luminal B	114	40.0
	Luminal B-Her2	30	10.5
	HER-2	19	6.7
	Triple-negative	32	11.2

These numbers reflect the failure to establish an efficient mammography screening system. For the sake of comparison, internationally, DCIS now represents about 20% of all breast cancers diagnosed by screening[20,21].

Other data obtained in this study reveal that most patients (71.5%) had their diagnosis established when they already had palpable clinical lesions, which may have a direct relation to prognosis, type of treatment performed, and costs to the health system. The type of lesion most often found was lump (89.0%), which corroborates other studies that showed that the most associated sign of breast cancer is the breast nodule[12,22]. The presence of a nodule larger than or equal to 2 cm is related with increased risk of breast cancer[23]. In the present study, the average tumor size at diagnosis was 28.6 mm, which is not in line with a good early diagnosis strategy. The clinical examination of the breasts performed by trained health professionals associated with mammography remains the best strategy for diagnosis in women at usual risk. However, the low number of screening mammograms in Brazil reflects on the rates of diagnosis already with clinically identified lesions. It is also known that breast self-examination is not recommended as a cancer screening method and has not shown effectiveness in reducing mortality from BC, which further reinforces the need for organized screening programs in Brazil[24]. Recently, a large study carried out in Mumbai, India, has found that clinical breast examination conducted every two years by primary health workers significantly downstaged breast cancer at diagnosis, but with a non-significant 15% overall reduction in breast cancer mortality[25].

Nulliparity is recognized as a risk factor for the development of the disease. Nevertheless, in our study, only 14.4% of diagnosed patients had this condition. Pregnancy and lactation are considered important protective factors for breast cancer. In our analysis, most patients had such conditions: 71.6% of patients were multiparous and 77.2% had a history of breastfeeding. This information highlights the diversity of factors involved and their real weight in the development of a breast cancer.

A family history of breast cancer is also a crucial factor associated with an increased risk of BC. Approximately 16% of patients diagnosed with breast cancer report a first-degree relative affected by the same condition[17]. The data from our study showed a positive family history of breast cancer in 17.0% of the cases, numbers that are in agreement with other studies, such as Barboza ***et al***, in which 1,176 Brazilian patients were analyzed, and most had no cases of breast cancer in the family[26]. The positive family history of breast cancer in a minority of cases does not justify screening based on this circumstance by itself, requiring more careful risk assessment.

Data from the present study show that 25.0% of patients were smokers. It is noteworthy that carcinogens found in tobacco are transported to the breast tissue, increasing the likelihood of mutations in oncogenes and suppressor genes (p53 in particular). Moreover, a long smoking history and smoking before the first full-term pregnancy are additional risk factors, more pronounced in women with a family history of breast cancer[17]. Although it is controversial, the association between smoking and breast cancer is evidenced in several studies[3].

Axillary lymph node involvement is a prognostic marker in the management of BC, and sentinel lymph node biopsy is an important part of tumor staging[27]. Axillary lymph node clinical involvement was observed in 43.1% of cases (n=121), whereas 56.9% (n=160) of patients had no suspicious axillary lymph node at diagnosis. The National Surgical Adjuvant Breast and Bowel Project (NSABP) in B-32 trial reported 29% of sentinel lymph node positivity, while in specialized centers, and with effective screening, the positivity rate is dropping below 20%[28,29]. Such data reinforce the importance of the cyto/histological diagnosis of the axillary status, due to the considerable false positive and false negative results of the axilla clinical examination. In cases of histological lymph node involvement, late diagnosis negatively impacts survival, in addition to worsening quality of life when lymphadenectomy is performed.

The histological classification known as the Nottingham Classification System is a recommended grading system to help determine the prognosis of BC[30]. Several studies have shown that patients with histological grade 1 have the best prognosis, while grade 3 tumors have the worst prognosis[31]. In the present study, it was found that 13.0% (n=37) of the tumors diagnosed were histological grade 1, whereas most of the cases, 59.4% (n=170), were grade 2 and the other 27.6% (n=79) were classified as grade 3.

We observed that a smaller proportion of cases were diagnosed in early stages (stage 0 and I): 32,3%. Stage IIA was the most found, with 28.9% of cases (n=84), followed by IA with 24.4% (n=71), and IIB with 17.2% of diagnoses (n=50). These data are aligned with a previous descriptive study conducted in this same health center in the countryside of Minas Gerais, through the analysis of 112 cases of BC diagnosed between 2008 and 2013, which revealed stage II as the most common at diagnosis[12]. Dugno *et al.*, in a cross-sectional study with 273 patients in a hospital in southern Brazil, found that most patients had the disease diagnosed in stages I and II (70.8% of cases; 36.6%, and 34.2%, respectively)[32]. Similarly, Simon ***et al.*** observed in a retrospective cohort of 2,296 women with histologically proven breast cancer that more than half (53.5%) of cases were stage II at diagnosis[16]. On the other hand, such data also reflect the heterogeneity of BC in Brazil, given that another cohort of patients with BC treated surgically at *Hospital das Clínicas* in Belo Horizonte showed that the stage at diagnosis was higher among patients in the public health system compared with diagnoses made in the private system (58% of cases in the public health services were diagnosed in the initial stages and 42% in stage III, while in the private system 86.4% were detected in the initial stages and only 17.6% in stage III)[33]. We found a small number of cases in stages IIIB (6.2%), IIIC (1.7%) and IV (2.4%). These data

may reflect a possible bias related to the search or direct referral to a specialized oncology center, without the primary assessment in our service, in advanced cases. Possibly, the low rate of stage IV tumors is due to the fact that patients did not pass through our service. Our microregion has a reference center in oncology, located in another city, that offers surgeries, systemic treatment and radiotherapy, and some patients are referred directly to this center by their cities.

In Brazil, laws define the maximum period of 30 days between the diagnostic hypothesis of BC and the confirmation through exams necessary for elucidation, and of 60 days between diagnosis and the beginning of treatment[34]. In our study, it was found that the mean time between the first visit to the mastologist and the histological diagnosis of BC was 63.2 days, and the mean time between histological diagnosis and the beginning of treatment was 39.6 days. In a recent study conducted by Gioia *et al.* in Rio de Janeiro, Brazil, the mean time to start treatment was 39 days[35]. It can be perceived in our study that the beginning of the treatment is within what is recommended by law; however, as observed in other studies, a delay is identified concerning the time of diagnosis of BC, with reports of the average delay reaching 142.5 days in other Brazilian surveys[36]. We think that our delay in obtaining the diagnosis can be, in part, reduced with the adoption of a patient navigation process.

According to the World Health Organization, there are three main steps to early diagnosis: awareness of the cancer symptoms and getting medical care (access interval); clinical evaluation, diagnosis and staging (diagnostic interval); and transition to treatment (treatment interval)[37]. Strategies focused on reducing delays between the detection of the first sign or symptom and treatment initiation should address the delays in all these steps. Implementing a BC patient navigation program has great potential to alleviate the barriers faced by patients in the public sector, and improve the outcomes of patients with BC in Brazil.

It is important to note that the data found in the present study are limited by their retrospective methodology and the restricted number of participants. However, such data contribute to the discussion about the strategy of mammographic screening in a younger age range in comparison with the current recommendation of the Ministry of Health, considering the significant prevalence of cases in the 40–49-year-old age group, in addition to improving the coverage of mammography screening across the target population. Additionally, it was observed that there is still a delay between the first visit to a specialist and the histological diagnosis of the lesion, suggesting that the diagnostic strategy is not ideal, since a considerable portion of BC cases could have been diagnosed even earlier and faster.

CONCLUSION

This study showed an important number of cases of BC in women who have not reached the age range recommended for the beginning of screening. Although they do not correspond to the majority of cases, they deserve attention because of their significant observance in the total number of women affected in our microregion. There was a high number of diagnoses with palpable tumors, a considerable rate of disease with lymph node involvement and a longer time interval for obtaining the histological diagnosis, contributing to the rates of disease in advanced stages. The need for improvements in the performance of mammographic screening was demonstrated, aiming at early diagnosis, in addition to mechanisms that optimize patient navigation.

AUTHORS' CONTRIBUTION

CFH: Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. CMR: Investigation, Methodology, Project Administration, Supervision, Validation, Visualization, Writing – original draft. ACOP: Investigation, Methodology, Validation, Visualization, Data curation. CACS: Data curation, Formal Analysis, Investigation, Validation, Writing – original draft. PHL: Data curation, Investigation, Visualization, Writing – review & editing. AOP: Data curation, Investigation, Visualization, Writing – review & editing. SMCR: Data curation, Investigation, Visualization, Writing – review & editing.

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https://doi.org/10.29289/2594539420220036ERRATUM

In the manuscript "Axillary surgical approach in T1-T2N0M0 clinical breast cancer staging: Survival in a women's hospital cohort in Rio de Janeiro", DOI: 10.29289/2594539420220036, published in the Mastology 2022;32:e20220036, on pages 4-5:

Where it reads:

Table 1. Distribution of sociodemographic and clinicopathologic status and treatment characteristics, according to axillary approach of the cohort of 827 women with breast cancer, treated at the Brazilian National Cancer Institute (2007–2009).

	Total*	Axillary surgery n(%)		χ^2
	n (%)	SLNB	SLNB+AL[a]	p-value
Age				
<40	54 (6.5)	41 (6.0)	13 (9.0)	0.049
40–59	426 (51.5)	343 (50.2)	83 (57.6)	
≥60	347 (42.0)	299 (43.8)	48 (33.3)	
Skin color				
Non-White	267 (32.3)	229 (33.5)	38 (26.4)	0.096
White	560 (67.7)	454 (66.5)	106 (73.6)	
Marital status				
With a partner	431 (52.1)	346 (50.7)	85 (59.0)	0.068
No partner	396 (47.9)	337 (49.3)	59 (41.0)	
Schooling				
<8 years	350 (42.4)	296 (43.3)	54 (37.8)	0.220
≥8 years	476 (57.6)	387 (56.7)	89(62.2)	
Occupation				
Unemployed	32 (3.9)	28 (4.1)	4 (2.8)	0.482
External job	372 (45.3)	301 (44.5)	71 (49.3)	
At home	417 (50.8)	348 (51.4)	69 (47.9)	
Alcoholism				
No	597 (73.0)	487 (72.1)	110 (76.9)	0.243
Yes	221 (27.0)	188 (27.9)	33 (23.1)	
Smoking				
No	562 (68.2)	467 (68.6)	95 (66.4)	0.617
Yes	262 (31.8)	214 (31.4)	48 (33.6)	
BMI				
Low weight	35 (4.2)	30 (4.4)	5 (3.5)	0.583
Suitable weight	227 (27.4)	193 (28.3)	34 (23.6)	
Overweight	297 (35.9)	244 (35.7)	53 (36.8)	
Obesity	268 (32.4)	216 (31.6)	52 (36.1)	
Clinical staging				
T1N0M0 (I)	543 (65.7)	478 (70.0)	65 (45.1)	0.000
T2N0M0 (IIA)	284 (34.3)	205 (30.0)	79 (54.9)	
Tumor size				
T1	566 (68.5)	495 (72.6)	71 (49.3)	0.000
T2	253 (30.6)	184 (27.0)	69 (47.9)	
T3	7 (0.8)	3 (0.4)	4 (2.8)	
Histological type				
Lobular Invasive	52 (6.3)	40 (5.9)	12 (8.3)	0.249
Ductal Invasive	713 (86.2)	588 (86.1)	125 (86.8)	
Others	62 (7.5)	55 (8.1)	7 (4.9)	
Histological grade				
1	166 (22.7)	145 (24.2)	21 (16.0)	0.038
2	293 (40.1)	243 (40.6)	50 (38.2)	
3	271 (37.1)	211 (35.2)	60 (45.8)	
Number of lymph nodes removed				
1–3	619 (74.8)	619 (90.6)	0 (0.0)	0.000
4–10	72 (8.7)	64 (9.4)	8 (5.6)	
>10	136(16.4)	0 (0.0)	136 (94.4)	
Lymph node status				
No metastasis				
With metastasis				

Continue...

Table 1. Continuation.

	Total*	Axillary surgery n(%)		χ^2
	n (%)	SLNB	SLNB+AL[a]	p-value
Sentinel lymph node metastasis				
No metastasis	699 (84.5)	666 (97.5)	33 (22.9)	0.000
Micrometastasis	41 (5.0)	17 (2.5)	24 (16.7)	
Macrometastasis	87 (10.5)	0 (0.0)	87 (60.4)	
Status HER2[b]				
Negative	368 (74.8)	295 (75.4)	73 (72.3)	0.366
Positive	70 (14.2)	57 (14.6)	13 (12.9)	
Indeterminate	54 (11.0)	39 (10.0)	15 (14.9)	
Hormonal receptor				
Positive	694 (84.7)	564 (83.6)	130 (90.3)	0.042
Negative	125 (15.3)	111 (16.4)	14 (9.7)	
Triple negative[b]				
No	436 (90.8)	343 (89.8)	93 (94.9)	0.118
Yes	44 (9.2)	39 (10.2)	5 (5.1)	
Other primary cancer				
No	812 (98.2)	672 (98.4)	140 (97.2)	0.340
Yes	15 (1.8)	11 (1.6)	4 (2.8)	
Death				
No	794 (96.0)	659 (96.5)	135 (93.8)	0.127
Yes	33 (4.0)	24 (3.5)	9 (6.2)	
Lymph node status				
No metastasis	699 (84,5)	666 (97,5)	33 (22,9)	0,000
With metastasis	128(15,5)	17 (2,5)	111 (77,1)	
Locoregional recurrence				
No	808 (97.7)	665 (97.4)	143 (99.3)	0.158
Yes	19 (2.3)	18 (2.6)	1 (0.7)	
Distance recurrence				
No	790 (95.5)	657 (96.2)	133 (92.4)	0.043
Yes	37 (4.5)	26 (3.8)	11 (7.6)	
Breast surgery				
Conservative	484 (58.5)	423 (61.9)	61 (42.4)	0.000
Mastectomy	343 (41.5)	260 (38.1)	83 (57.6)	
Breast reconstruction				
No	681 (82.3)	557 (81.6)	124 (86.1)	0.192
Yes	146 (17.7)	126 (18.4)	20 (13.9)	
Chemotherapy				
No	409 (49.5)	381 (55.8)	28 (19.4)	0.000
Yes	418 (50.5)	302 (44.2)	116 (80.6)	
Radiotherapy				
No	328 (39.7)	265 (38.8)	63 (43.8)	0.270
Yes	499 (60.3)	418 (61.2)	81 (56.2)	
Hormonal therapy				
No	169 (20.4)	150 (22.0)	19 (13.2)	0.018
Yes	658 (79.6)	533 (78.0)	125 (86.8)	
Target therapy				
No	790 (95.5)	655 (95.9)	135 (93.8)	0.257
Yes	37 (4.5)	28 (4.1)	9 (6.2)	
Severity score[c]				
0–1	78 (9.4)	78 (11.4)	0 (0.0)	0.000
2–4	675 (81.6)	573 (83.9)	102 (70.8)	
5–6	74 (8.9)	32 (4.7)	42 (29.2)	

SLNB: sentinel lymph node biopsy; AL: axillary lymphadenectomy; BMI: body mass index; HER2: human epidermal growth factor receptor 2; χ^2: Pearson's χ^2 test; Non-white: black, brown. *The total value may change due to missing values. [a]Sentinel lymph node biopsy with a subsequent axillary lymphadenectomy. [b]The analysis of molecular markers has become routine at Brazilian National Cancer Institute starting 2011, not all patients underwent the tests. [c]Severity score includes age, clinical staging, histological grade, and lymph node status.

It should read:

Table 1. Distribution of sociodemographic and clinicopathologic status and treatment characteristics, according to axillary approach of the cohort of 827 women with breast cancer, treated at the Brazilian National Cancer Institute (2007–2009).

	Total*	Axillary surgery N(%)		x^2
	n (%)	SLNB	SLNB+AL[a]	p-value
Age				
<40	54 (6.5)	41 (6.0)	13 (9.0)	0.049
40–59	426 (51.5)	343 (50.2)	83 (57.6)	
≥60	347 (42.0)	299 (43.8)	48 (33.3)	
Skin color				
Non-White	267 (32.3)	229 (33.5)	38 (26.4)	0.096
White	560 (67.7)	454 (66.5)	106 (73.6)	
Marital status				
With a partner	431 (52.1)	346 (50.7)	85 (59.0)	0.068
No partner	396 (47.9)	337 (49.3)	59 (41.0)	
Schooling				
<8 years	350 (42.4)	296 (43.3)	54 (37.8)	0.220
≥8 years	476 (57.6)	387 (56.7)	89(62.2)	
Occupation				
Unemployed	32 (3.9)	28 (4.1)	4 (2.8)	0.482
External job	372 (45.3)	301 (44.5)	71 (49.3)	
At home	417 (50.8)	348 (51.4)	69 (47.9)	
Alcoholism				
No	597 (73.0)	487 (72.1)	110 (76.9)	0.243
Yes	221 (27.0)	188 (27.9)	33 (23.1)	
Smoking				
No	562 (68.2)	467 (68.6)	95 (66.4)	0.617
Yes	262 (31.8)	214 (31.4)	48 (33.6)	
BMI				
Low weight	35 (4.2)	30 (4.4)	5 (3.5)	0.583
Suitable weight	227 (27.4)	193 (28.3)	34 (23.6)	
Overweight	297 (35.9)	244 (35.7)	53 (36.8)	
Obesity	268 (32.4)	216 (31.6)	52 (36.1)	
Clinical staging				
T1N0M0 (I)	543 (65.7)	478 (70.0)	65 (45.1)	0.000
T2N0M0 (IIA)	284 (34.3)	205 (30.0)	79 (54.9)	
Tumor size				
T1	566 (68.5)	495 (72.6)	71 (49.3)	0.000
T2	253 (30.6)	184 (27.0)	69 (47.9)	
T3	7 (0.8)	3 (0.4)	4 (2.8)	
Histological type				
Lobular Invasive	52 (6.3)	40 (5.9)	12 (8.3)	0.249
Ductal Invasive	713 (86.2)	588 (86.1)	125 (86.8)	
Others	62 (7.5)	55 (8.1)	7 (4.9)	
Histological grade				
1	166 (22.7)	145 (24.2)	21 (16.0)	0.038
2	293 (40.1)	243 (40.6)	50 (38.2)	
3	271 (37.1)	211 (35.2)	60 (45.8)	
Number of lymph nodes removed				
1–3	619 (74.8)	619 (90.6)	0 (0.0)	0.000
4–10	72 (8.7)	64 (9.4)	8 (5.6)	
>10	136(16.4)	0 (0.0)	136 (94.4)	
Sentinel lymph node metastasis				
No metastasis	699 (84.5)	666 (97.5)	33 (22.9)	0.000
Micrometastasis	41 (5.0)	17 (2.5)	24 (16.7)	
Macrometastasis	87 (10.5)	0 (0.0)	87 (60.4)	

Continue...

Table 1. Continuation.

	Total*	Axillary surgery N(%)		x^2
	n (%)	SLNB	SLNB+AL[a]	p-value
Status HER2[b]				
Negative	368 (74.8)	295 (75.4)	73 (72.3)	0.366
Positive	70 (14.2)	57 (14.6)	13 (12.9)	
Indeterminate	54 (11.0)	39 (10.0)	15 (14.9)	
Hormonal receptor				
Positive	694 (84.7)	564 (83.6)	130 (90.3)	0.042
Negative	125 (15.3)	111 (16.4)	14 (9.7)	
Triple negative[b]				
No	436 (90.8)	343 (89.8)	93 (94.9)	0.118
Yes	44 (9.2)	39 (10.2)	5 (5.1)	
Other primary cancer				
No	812 (98.2)	672 (98.4)	140 (97.2)	0.340
Yes	15 (1.8)	11 (1.6)	4 (2.8)	
Death				
No	794 (96.0)	659 (96.5)	135 (93.8)	0.127
Yes	33 (4.0)	24 (3.5)	9 (6.2)	
Lymph node statu				
No metastasis	699 (84.5)	666 (97.5)	33 (22.9)	0.000
With metastasis	128(15.5)	17 (2.5)	111 (77.1)	
Locoregional recurrence				
No	808 (97.7)	665 (97.4)	143 (99.3)	0.158
Yes	19 (2.3)	18 (2.6)	1 (0.7)	
Distance recurrence				
No	790 (95.5)	657 (96.2)	133 (92.4)	0.043
Yes	37 (4.5)	26 (3.8)	11 (7.6)	
Breast surgery				
Conservative	484 (58.5)	423 (61.9)	61 (42.4)	0.000
Mastectomy	343 (41.5)	260 (38.1)	83 (57.6)	
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No	681 (82.3)	557 (81.6)	124 (86.1)	0.192
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